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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
ALLEMAGNE

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Combination of epinastine and an antioxidant vitamin as new pharmaceutical composition for the treatment of skin diseases

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Combination of epinastine and an antioxidant vitamin as new pharmaceutical composition for the treatment of skin diseases

The present invention relates to new pharmaceutical compositions for the treatment of skin diseases, comprising an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof as a pharmacologically active compound, and at least on vitamin having antioxidant properties. The formulations described in the present invention may include pharmaceutically acceptable carriers and excipients.

Moreover, the invention relates to the use of these formulations to treat pruritus (itching) derived from skin diseases such as urticaria, eczema and skin irritation. Remarkably, the formulations described in the present invention are highly effective in the treatment of skin diseases associated with allergic reactions.

Background of the invention

In recent years, the incidence of developing skin diseases associated with allergic reactions has increased due to changes in diet, changes of the life style, air pollution, increased exposure to environmental chemicals from numerous environmental deterioration, stress in the social life and so on. Among these allergic reactions are urticaria, eczema, skin irritation and dermatitis as well as skin diseases accompanying itching represented by pruritus, prurigo, psoriasis vulgaris etc.

Urticaria, a synonym of wheal, is a transient edema. The disease is characterized by a sudden onset of itchy sensation on skin, followed by developing well defined eruption swelling up like weal and growing into a size of nail plate to palm exacerbated by scratching. Although the symptoms disappear within a couple of minutes to hours and may not leave any skin disorder, episodes of development into eruption are likely to recur. Causes of urticaria may include autosensitization, sensitizations associated with difficult menstruation, pregnancy, foods, medicines and insect stings, abnormal responses to heat, cold, mechanical stimuli and light, remote responses to bacterial infections, gastrointestinal, hepatic, and renal disease, an endocrinopathic involvement, and psychological factors.

Eczema or dermatitis is the most major skin disease, characterized by inflammatory response on skin. Eczema and dermatitis are often referred altogether as eczematous dermatitis group. The diseases are often caused by pathological interactions caused by external stimuli (numbers of chemicals, fragrances, metals, detergents, medicines, plants, bacteria, insects, sunlight, heat, cold, dryness), internal abnormalities (local abnormalities such as perspiration, abnormal sebum secretion, abnormal keratosis, and systemic abnormalities such as atopic disposition, infection site, digestive disorder, renal dysfunction, endocrine disturbance), and bodily condition. Eczematous dermatitis group includes contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular eczema, autosensitization dermatitis, and lichen simplex chronicus Vidal.

Housewives' eczema, keratodermia tylodes palmaris progressiva, diaper dermatitis, and photocontact dermatitis are classified as atypical contact dermatitis. In addition, the group may include diffuse neurodermatitis, stasis dermatitis, infectious eczematoid dermatitis, and perioral dermatitis. Broadly, it may also include radiodermatitis, scald (burn), and frostbite.

Pruritus is a disease characterized by an onset of itchy sensation (itching) on apparently normal skin. Range of affected lesion divides pruritus into universal pruritus and localized pruritus. The disease is derived from a variety of causes, and often develops as a symptom of systemic disease.

Prurigo presents extreme itching and is papule or urticaria-like nodule that progress to chronic or recurrent disorder, and can be broadly classified into prurigo acuta including strophulus infantum, lichen urticatus, prurigo aestiralis, prurigo simplex acuta, prurigo subacuta such as prurigo simplex subacuta, and prurigo chronica including chronica multiformis, prurigo nodularis, prurigo Hebra, and prurigo simplex chronica. Mechanisms of the pathogenesis are unrevealed. Insect sting in prurigo acuta, and diabetes mellitus, hepatopathy, leukemia, Hodgkin's disease, visceral cancer, and polycythemia in prurigo chronica are thought of as causatives.

Psoriasis vulgaris is an inflammatory skin disease, and presents histological

characteristics of epidermal hyperplasia and inflammatory cellular infiltration. Eruption typically develops on head, extension side of extremities, and some parts of truncus which are in particular likely to come in contact with mechanical compression, in almost a half of which pruritus is observed. Immunological abnormalities may be concerned as a cause of disease.

It is emphasized that improvements on surroundings such as eliminating causative antigens is the most important treatment of these skin diseases, particularly for allergic skin disease. Nevertheless, as already reviewed, pathogenic causes are complicated, and therefore are fallible to be identified. Consequently, compositions combining antihistaminic compounds are of the frequent choice for treatments of these symptoms including itchy sensation caused from skin diseases.

A liquid antitussive formulation composed of acetaminophen, dimemorfan phosphate, epinastine hydrochloride, dl- methylephedrine hydrochloride, bromhexine hydrochloride, lysozyme chloride, anhydrous caffeine, and vitamin C as pharmacological active compounds is disclosed in Example 5 of JP2001-097856A.

A liquid antitussive formulation composed of naproxen, dihydrocodeine phosphate, epinastine hydrochloride, dl- methylephedrine hydrochloride, bromhexine hydrochloride, lysozyme chloride, anhydrous caffeine, and vitamin as pharmacological active compounds is disclosed in Example 29 of JP2000-344682A.

A liquid medical composition having antitussive effect composed of fenoprofen, dihydrocodeine phosphate, epinastine hydrochloride, dl- methylephedrine hydrochloride, bromhexine hydrochloride, lysozyme chloride, anhydrous caffeine, and vitamin C as pharmacological active compounds is disclosed in Example 5 of JP11-071281A.

A liquid cough medicine comprising fenoprofen, dihydrocodeine phosphate, epinastine hydrochloride, dl- methylephedrine hydrochloride, ambroxol hydrochloride, anhydrous caffeine, and vitamin C as pharmacological active compounds is disclosed in Example 5 of JP11-071281A.

All these medicines are antitussive expectorant and cold remedies. The use thereof for the treatment of skin diseases has not been disclosed.

Objective of the present invention

The present invention aims to provide a compositions for the treatment of skin diseases that exert its significant utility to achieve effective improvements.
In addition, the present invention intends to provide the compositions for treatment of skin diseases by employing highly effective pharmaceutical compounds for significant improvements on symptoms of skin diseases accompanying itching, particularly urticaria, eczema, skin fit, dermatitis, pruritus, eruption, and psoriasis vulgaris accompanying itchy sensation.

Description of the invention

The invention relates to pharmaceutical formulations for the treatment of skin diseases comprising an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof as pharmacologically active compound, and at least one vitamin that has antioxidant properties. Such vitamins preferably are free radical scavenger.

Epinastine, (±) 3-amino-9, 13b-dihydro-1H-dibenz [c, f] imidazo [1,5-a] azepine, is a drug possessing H1-antihistaninic property. It primarily has been used to treat allergic reaction of the eyes and the nasal mucosa.

In the composition of the present invention Epinastine preferably is taken in the form of a salt such as the hydrochloride, hydrobromide, oxalate, nitrate, sulfonate, fumarate, maleate, sulfate, and phosphate. The free base can be taken, too. Preferred is Epinastine-hydrochloride.

The amount of epinastine or a pharmacologically acceptable salt thereof depends on the application route.

In the case of oral application, the daily dosage in equivalent quantity of Epinastine-

hydrochloride for an adult is between 2 and 20, preferably between 5 and 15 mg, and further more preferably between 7.5 and 12.5 mg. Preferably , this amount is given via one or more tablets.

In the case of topical application the amount in equivalent quantity of Epinastine hydrochloride is between 1 and 50 mg per 1 g of composition, preferably between 2 and 30 mg per 1 g of composition, and further more preferably between 5 and 15 mg per 1 g of composition.

The inventive formulations includes at least one antioxidant vitamin in addition to Epinastine.

There is no particular restriction in types of the antioxidant vitamin(s) to be together with Epinastine provided that the corresponding vitamin(s) has (have) antioxidant properties.

In the context of the present invention preferred examples include vitamin C, vitamin E, vitamin A, and such vitamin-like active substances.

Concerning the vitamin C / vitamin C -like active substances, the at least one vitamin having antioxidant properties preferably may be selected from one or more of the following group: ascorbic acid, metallic ascorbate, such as sodium ascorbate, potassium ascorbate, calcium ascorbate, magnesium ascorbate, aluminum ascorbate, ascorbic acid derivative, such as ascorbyl phosphates, in particular sodium or potassium ascorbyl phosphate, magnesium ascorbyl phosphate, calcium ascorbyl phosphate, and aluminum ascorbyl phosphate, ascorbic sulfates such as disodium ascorbyl sulfate, potassium ascorbyl sulfate, magnesium ascorbyl sulfate, calcium ascorbyl sulfate, and aluminum ascorbyl sulfate, ascorbyl glucosides such as ascorbyl-2-glucoside, ascorbyl fatty acid glucosides, ascorbyl fatty acids, erythorbic acid (isoascorbic acid), and metallic erythorbate, such as sodium erythorbate.

Examples of vitamin E / vitamin E -like active substances comprise d-α-tocopherol, dl-α-tocopherol, d-α-tocopherol acetate, dl-α-tocopherol acetate, d-α-tocopherol

succinate, dl-α-tocopherol succinate, dl-α-tocopherol calcium succinate, tocopherol nicotinate, vitamin E linoleate (preferably a mixture of tocopheryl esters, mainly tocopheryl linoleate), dl-βtocopherol, dl-γtocopherol, d-δ-tocopherol, and natural mixed tocopherol.

Examples of vitamin A / vitamin A -like active substances comprise vitamin A, retinal acetate, retinol palmitate, retinol etretinate, vitamin A oil, cod liver oil, strong cod liver oil, and also carotene such asα-carotene, β-carotene, γ-carotene, and lycopene can be added to the above.

Examples of other vitamin-like active substance which has antioxidant properties comprise of ubiquinone (coenzyme Q, ubidecarenone), pangamic acid, and flavonoids.

One or more compounds of these antioxidant vitamins can be used to formulate this invention. Preferably the composition contains only one of the named vitamins.

For combinations of Epinastine plus two vitamins the combinations with

- vitamin C plus vitamin E,
- vitamin C plus vitamin A, and
- vitamin C plus such vitamin-like active substances
- vitamin E plus vitamin A, and
- vitamin E plus such vitamin-like active substances

are preferred.

For combinations of Epinastine plus three vitamins the combinations with

- vitamin C, vitamin A and vitamin E

are preferred.

Furthermore, other pharmaceutical active substances can be combined to formulate this invention. Examples comprise sulfur amino acids such as cysteine, methionine, aminoethylsulfonic acid or glutathione. Other examples are vitamin D such as ergocalciferol and cholecalciferol. However, teh combinaiton also may comprise any

other kind of vitamin or vitamin mixture.

In the formulation of the present invention the amount of the at least on antioxidant vitamin varies depending on the type of the antioxidant vitamin. For daily oral use for an adult, it lies in the range of from 0.01 to 3000 mg, and for topical use, it lies in the range of from 0.1 to 200 mg/g.

In particular, the daily dosage range for a vitamin C, given orally to an adult lies in the range of from 5 to 3000 mg, preferably in the range of from 25 to 2000 mg, and more preferably in the range of from 50 to 500 mg, and for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 5 to 40 mg/g.

The daily dosage range for a vitamin E, given orally to an adult lies in the range of from 1 to 500 mg, preferably in the range of from 5 to 300 mg, and more preferably in the range of from 10 to 100 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 60 mg/g, and more preferably in the range of from 0.5 to 30 mg/g.

The daily dosage range for a vitamin A, given orally to an adult lies in the range of from 10 to 10000 IU (international unit), preferably in the range of from 100 to 4000 IU, and more preferably in the range of from 500 to 2000 IU. And for topical use it lies in the range within 200000 IU/g, preferably in the range of from 100 to 50000 IU/g, and more preferably in the range of from 1000 to 10000 IU/g.

The daily orally to an adult given dosage range for ubiquinone, (coenzyme Q, ubidecarenone), which is vitamin-like active substance lies in the range of from 1 to 300 mg, preferably in the range of from 3 to 150 mg, and more preferably in the range of from 6 to 30 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 1 to 15 mg/g.

The daily dosage range for a pangamic acid, given orally to an adult lies in the range of from 2 to 1000 mg, preferably in the range of from 10 to 500 mg, and more preferably in the range of from 20 to 100 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 1 to 15 mg/g.

The daily dosage range for a flavonoid, given orally to an adult lies in the range of from 6 to 1500 mg, preferably in the range of from 30 to 600 mg, and more preferably in the range of from 60 to 300 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 1 to 15 mg/g.

It is possible that the pharmaceutical compositions described in the present invention are given orally or topically all at once or in divided portions. Topically the formulaiton is applied directly onto the affected region of skin. Dose adjustment of Epinastine and antioxidant vitamins may reflect age, body weight, and manifesting symptoms.

The pharmaceutical compositions described in the present invention can be used in any oral form such as tablets, granules, subtle granules, powders, capsules, caplets, soft capsules, pills, suspensions, emulsions, oral solutions, syrups, dried syrups, chewable forms, forming tablets, drops, and orally disintegrable tablets, and in any topical form such as creams, ointments, gel ointments, suppositories, poultices, tapes, topical solutions, aerosols, lotions, and foams. In addition, preparation formed into microparticles such as microcapsule, nanocapsules, microspheres, nanospheres, liposomes may be also included in the aforementioned compositions.

Moreover, functions can be added using preparation additive: improvement in stabilization, slow release, continuance, quickly distinglation, quickly dissolution and dissolution of medicinal properties, concealment of taste, improvement in usage. Adding these functions can be done by the usual manner. For example: dispensing pharmaceutically active substance in a separate granule, making multi-layer granules, multi-layer tablets or dry coated tablet, tablets by separating granules,

microcapsules, coating preparations such as sugarcoated tablets, film coating tablets, coating granule, foaming pharmaceutical preparation, chewable preparation, dissolving preparation in the mouth, matrix preparation, together comminution, making solid solution, adding sweetening agent, refrigerant, antioxidant or stabilizing agent, adjust to certain pH, viscosity, osmotic pressure, salt concentration. These methods can be combined.

It is acceptable that, if necessary, these compositions combine with pharmaceutically acceptable additives which follow; excipients, bases, binders, disintegrators, lubricants, superplasticizers, coating agents, sugar coating agents, plasticizers, antifoaming agents, polish, foaming agents, antistatic agents, desiccant, moisturizing agents, surfactant, solubilizer, buffer agents, resolvents, solubilizing agents, solvents, diluents, stabilizers, emulsifying agents, suspension, suspending agents, dispersing agents, isotonizing agents, aerosol propellant, adsorbents, reducing agents, antioxidant, backing, wetting agents, wet modifier, filler, extender, adhesives, viscous agent, softeners, pH modifiers, antiseptics, preservatives, sweetening agents, corrigent, refrigerative agents, flavoring agents, perfume, fragrance, coloring matters, bitter taste masking agents and the like. Any of these additives may be used in the regular compositions methods, and do not impose any limitation to such composition methods.

The examples of these additives are explained in the Japanese Pharmaceutical Excipients Directory 2000 (Japan Pharmaceutical Excipients Council edit, Yakuji Nippo. Ltd. issue).

These preparations can be manufactured in the usual manner by adding the preparation additives to the pharmacologically active substance or any other method.

The compositions described in the present invention are explained now by examples. However, the present invention of the pharmaceutical compositions is not limited to these examples.

Example 1

: Powder

The following ingredients were uniformly mixed. The resulted mixed particles were divided into 600 mg per one pack to prepare powder compositions.

Epinastine hydrochloride	10 g
Calcium ascorbate	180 g
L-cysteine	160 g
Corn starch	530 g
Lactose	900 g
Magnesium stearate	20 g

Example 2

: Granules

The following ingredients were prepared into granules through a regular method to prepare mixed particles, and packed to give amount of 1000 mg per one pack for granules.

Epinastine hydrochloride	10 g
Ascorbic acid	250 g
Calcium ascorbate	250 g
Riken Dry A-S200PT (Vitamin A 200,000 I.U./g)	0.01 g
dl- α-tocopherol calcium succinate	100 g
Ubiquinone	30 g
Pangamic acid	50 g
Flavonoid	100 g
Calcium carboxymethylcellulose	240 g
Mannitol	1300 g
Corn starch	527.99 g
Tartaric acid	100 g
Aspartame	20 g
Acesulfame potassium	20 g
Fragrant materials	2 g

Example 3

: Tablet

The following ingredients were uniformly mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Epinastine hydrochloride	30 g
dl- α-tocopherol calcium succinate	250 g
Ubiquinone	75 g
Lactose	310 g
Microcrystalline cellulose	575 g
Light anhydrous silicic acid	5 g
Talc	5 g
Magnesium stearate	5 g

Example 4

: Tablet

The following ingredients were uniformly mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Epinastine hydrochloride	20 g
Ascorbic acid	100 g
dl- α-tocopherol calcium succinate	100 g
Riken Dry A-S200PT (Vitamin A 200,000 I.U./g)	0.02 g
Lactose	455.98 g
Microcrystalline cellulose	600 g
Light anhydrous silicic acid	12 g
Talc	6 g
Magnesium stearate	6 g

Example 5

: Oral solution

The following ingredients were dissolved into a portion of sterile purified water, added with sodium hydrate to adjust at pH 5, and diluted with sterile purified water to make total volume of 20 L. The resulted solution was transferred by 50 mL into glass bottles to provide oral solutions.

Epinastine hydrochloride	4 g
Ascorbic acid	40 g
Aminoethylsulfonic acid	400 g
Citric acid	50 g
Sodium citrate	10 g
Purified sucrose	2400 g
Caramel	60 g
Sodium hydrate	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 6

: Cream

The following ingredients were processed through a regular method to form cream at the total weight of 1kg, added with sodium citrate to adjust at pH 5.

Epinastine hydrochloride	10.0 g
dl- a-tocopherol acetate	5.0 g
Vitamin A oil: vitamin A 100000 I.U./g	2.0 g
Medium chain fatty acid triglyceride	200.0 g
Propylene glycol	150.0 g
Glyceryl monostearate	80.0 g
Polyoxyethylene cetyl ether	40.0 g
Diisopropyl adipate	50.0 g
Citric acid	0.1 g
Sodium citrate	Adequate amount
Antiseptics	Adequate amount
Purified water	Adequate amount

Claims

1. A pharmaceutical formulation for the treatment of skin diseases, comprising Epinastine or a pharmaceutically acceptable salt thereof as pharmacologically active compound, and at least on vitamin with antioxidant properties.

2. The pharmaceutical formulation according to claim 1, characterised in that the daily amount of Epinastine or its pharmaceutically acceptable salt thereof for oral use if given to an adult lies in the range of from 2 to 20 mg in equivalent quantity to Epinastine hydrochloride.

3. The pharmaceutical formulation according to claim 1, characterised in that the amount of Epinastine or a pharmaceutically acceptable salt thereof if applied topically lies in the range of from 1 to 50 mg in equivalent quantity to Epinastine chloride per 1 g of the formulation.

4. The pharmaceutical formulation according to claim 1, characterised in that the daily dose of the at least one antioxidant vitamin lies in the range of from 1 to 3000 mg.

5. The pharmaceutical formulation according to claim 1, characterised in that the amount of the at least one antioxidant vitamin if applied topically lies in the range of from 0.1 to 200 mg per 1 g of the formulation.

6. The pharmaceutical formulation according to claim 1, characterised in that the at least one antioxidant vitamin is selected from vitamin C, vitamin E, vitamin A, and/or vitamin-like active substance.

7. The pharmaceutical formulation according to claim 1, characterised in that the formulation comprises at least two antioxidant vitamins.

8. The pharmaceutical formulation according to claim 1, characterised in that the formulation comprises at least three antioxidant vitamins.

9. Use of a formulation according to any of claims 1 to 8 for the manufacture of a medicament for the treatment of skin diseases.

10. Use according to claim 9 for the manufacture of a medicament for the treatment of skin diseases associated with allergic reactions.

11. Method for the treatment of a skin disease, in particular skin diseases associated with allergic reactions, whereby the method comprises applying a pharmaceutical formulation according to any of claims 1 to 8.

Abstract

The invention relates to a new pharmaceutical formulation for the treatment of skin diseases, comprising an antihistaminic-effective amount of Epinastine or pharmaceutically acceptable salt thereof as pharmacologically active compound, and vitamins that have antioxidant (free radical scavenger) properties. The formulations described in the present invention additionally include pharmaceutically acceptable carriers and excipients.

The invention further relates to the use of these formulations indicated to pruritus (itching) derived from skin diseases such as uriticaria, eczema, and skin irritation.

Remarkably, among a variety of symptoms derived from skin diseases, the invention exerts its high therapeutic utility to skin diseases associated with allergic reactions.